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ADDENDUM

LIST OF THE CLINICAL CONTRIBUTIONS OF HUGH HUGER TOLAND, M.D. (1806-1880)

(For list see back advertising section, page 45 in this issue)

CLINICAL NOTES AND CASE REPORTS

HEMOPOIETIC APLASIAS FOLLOWING THE ARSPHENAMINS, WITH TWO CASE REPORTS

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DURING the past few years the arsphenamins have been belabored because of untoward results occurring during the treatment of syphilis. Among these unlooked-for complications, changes in the hemopoietic system, due to the arsphenamins, have more and more been frequently mentioned. This increasing accumulation of literature is probably due in part to several masterful articles appearing during 1932. McCarthy [1] and Wilson published a summary of the literature, and cited two cases of symptomatic theombocytopenic purpura at about the same time that A. B. Loveman [2] also reviewed the literature and added several cases of varied types of blood reactions due to the arsphenamins. These conditions are rare, however. Cole [3] and his coworkers observed only two cases of blood dyscrasias in a total of 338 complications arising in the treatment of 1,212 patients over a ten-year period. Phelps had two cases in 272,354 injections, and Combs one in 4,000 patients. The following two cases have occurred in our antiluetic clinic in some 23,000 injections over a period of six years.

REPORT OF CASES

CASE 1.—T. A., a seaman, white, age forty-two, reported at the outpatient clinic of the Marine Hospital at San Francisco, California, on October 7, 1935, complaining of a penile lesion which had been present, off and on, for the past six months. Blood was obtained for a Wassermann test on that date. The Noguchi antigen was one plus, the cholesterin antigen was four plus, and the Kahn test was positive. The patient stated that he had had no previous treatment. He had gonorrheal urethritis in 1931.

As no contraindications were present, antiluetic therapy was started at once, with prompt healing of the penile lesion. During the course of his outpatient treatment he received twenty-one intramuscular injections of bismuth, totaling 3.15 grams, and twenty-one intravenous injections of neoarsphenamin, totaling 8.55 grams.

On January 15, 1936, however, after receiving his treatment, he complained of nose-bleeds, which had been occurring off and on for the past two weeks. He had also had a cold, with cough, for one week. He was at once sent to the ear, nose, and throat clinic, where a small oozing point was discovered on the septum. The nose was packed with cocain-oxycyanid, the packing being removed on the following day. He returned on January 20, four days after this, when he stated that the bleeding had reappeared and had become almost constant. He was admitted to the hospital on the medical service.

On admission, the patient's only complaints were bleeding from the nose and a cold with coughing. Physical examination revealed the following significant findings:

A moderately obese white male, quite apprehensive, with clotted blood on his lips and bright red blood oozing from his nares.

Eyes: Conjunctiva injected. Definite icteric tint to sclerae. Pupils equal and regular, and react to light and in accommodation. Extra-ocular movements normal.

Nose: Both nostrils filled with fresh blood-clots. Blood oozing from under clots. No bleeding points seen after clots were removed.

Mouth: Lips coated with dried blood. Tongue coated. Petechial spots on palate and on buccal mucous membrane. Pharynx injected and tonsils atrophic. Several ulcerative lesions on uvula and soft palate.

Neck: No adenopathy present.

Heart: Apex impulse in fifth interspace one centimeter outside midclavicular line, rate 68, regular rhythm. No thrills. Soft, blowing systolic murmur heard at aortic area. Blood pressure, 120/80.

Lungs: A few subcrepitant râles heard scattered throughout both lung fields. Otherwise examination was negative.

Abdomen: Obese. No scars, hernias, masses, tenderness, or rigidity. Liver not enlarged or tender. Spleen barely palpable.

Extremities: A few small petechial spots on the right arm and under several fingernails of both hands.

Laboratory work and treatment were immediately started, using the following possibilities as a working diagnosis:

1. Arsenical reaction.
2. Blood dyscrasia.
3. Bacterial endocarditis.

The appended chart indicates the blood picture from day to day, with the accompanying treatment:

COMMENT

The blood culture was found to be negative, and as there was a history of intensive arsenical treatment for the past three months, it seemed evident that the accompanying blood dyscrasia could be best explained on a basis of neoarsphenamin as the etiologic agent. Due to the marked reduction in polymorphonuclear cells, agranulocytosis was thought of at once. There was, seemingly, one serious discrepancy in this diagnosis,

CHART 1.—*Day by Day Blood Picture*

Date	R. B. C.	W. B. C.	Hgb.	Plate	Differential	Remarks
1/20/36	4,100,000	4,400	75%	16,190	Polys 20 S. Lymphocytes 40 L. Lymphocytes 10 Transitionals 30	Icteric index 45 Bleeding time 13 Coagulation time 5 Blood culture Negative
1/21/36	.....	3,000	.....	.....	Polys 15 S. Lymphocytes 18 L. Lymphocytes 37 Transitionals 30	Liver extract started by mouth. Pentnucleotid 10 c. c. I. M.
2/22/36	4,100,000	2,900	73%	2,400	Polys 5 S. Lymphocytes 20 L. Lymphocytes 35 Transitionals 10	Pentnucleotid 30 c. c. I. M. Blood transfusion 480 c. c.
2/23/36	4,760,000	6,000	83%	.....	Polys 20 S. Lymphocytes 10 L. Lymphocytes 40 Transitionals 30	Pentnucleotid 30 c. c. I. M.
2/24/36 9:00 a. m.	.....	1,500	.....	500	Polys 0 S. Lymphocytes 18 L. Lymphocytes 42 Transitionals 40	No normal W.B.C. seen—all showing marked degeneration. Pentnucleotid 20 c. c. I. M.
4:00 p. m.	4,240,000	3,400	63%	.....	Polys 20 S. Lymphocytes 32 L. Lymphocytes 36 Transitionals 8 Rosin 4	Blood transfusion 210 c. c. 26 3:00 p. m. Patient expired at 12:00 midnight.

namely, the tremendous reduction in the blood platelet count, with the accompanying hemorrhagic diathesis. As the case was further studied, however, it was realized that arsphenamin may produce not only an agranulocytosis, but also a thrombocytopenic purpura, and even a complete aplasia of the bone marrow. The patient was, therefore, believed to have a combination of agranulocytosis and thrombocytopenic purpura, the etiologic agent being neoarsphenamin.

In considering the proper treatment to be employed, the question arose as to the extent of damage in the bone marrow. If an aplastic anemia were present the prognosis was, of course, exceedingly grave. There was, however, at no time any definite indication of this, the red-cell count never dropping below 4,000,000 in spite of continuous oozing of blood from the mucous membranes of the nose and throat and, probably, the intestinal tract. We believed, therefore, that we were justified in using large doses of pentnucleotide in combination with blood transfusions and liver extract. In spite of these measures, the bleeding became progressively worse, the polymorphonuclear cells dropped to zero, the blood platelets dropped to 500 centimeters, and the patient died at midnight on February 24, 1936, after being in the hospital less than five days.

NECROPSY REPORT

An obese white male, 65 inches tall, hair tinged with gray. There is a frothy, bloody fluid running from the nose and mouth. The pupils are contracted. Marked subconjunctival hemorrhage in both eyes. No external lymphadenopathy.

Chest: No fluid or adhesions in either pleural cavity. Lungs normal, except for hypostatic congestion of the bases.

Heart: Pericardial sac contains 50 cubic centimeters of clear serous fluid. Several petechiae are present on the epicardium. The left ventricle is pale, and hypertrophic. The valves are normal and the coronary orifices are patent. There are mild luetic changes in the intima of all parts of the aorta. The heart weighed 440 grams.

Abdomen: Obese wall. Tissues show icteric tint. Intestines distended with gas. Numerous purpuric areas present in the lower five feet of the ileum. The lumen contains black, tarry material, evidently partially digested blood.

Spleen: Weighs 240 grams. Is about twice normal size, dark mahogany in color, with numerous petechiae on the surface. It is mushy in consistency and, on sectioning, the surfaces are dark red with areas of hemorrhage present.

Liver: Petechial hemorrhages scattered over the whole surface. Sections show gross hemorrhages interspersed between yellow areas, suggestive of fatty degeneration.

Stomach: Contains about 300 cubic centimeters of a dark, bloody fluid. There are numerous petechial hemorrhages in the mucous membrane along the greater curvature.

Kidneys: Normal size. Both kidneys congested. The capsule strips easily. Petechial hemorrhages are present over the surface. In the cut surfaces the cortex is congested and edematous. Numerous hemorrhagic areas are present throughout the parenchyma.

Bone marrow: Pale in color. Microscopically, there is no evidence of any attempt at regeneration. Normoblasts greatly reduced per oil immersion field. Myelogenous series markedly reduced and very toxic in appearance, vacuolated, with no mature cells seen.

Pancreas, bladder, testicles and prostatic gland are normal.

* * *

CASE 2.—C. M., a seaman, white, age twenty-four years, entered the Marine Hospital at San Francisco, California, on November 28, 1934. He complained of a urethral discharge and penile sores. His family and personal history were not significant. He denied having taken coal-tar derivatives or any additional medication other than the antiluetic treatment mentioned below. Twenty-eight days previous to admission he developed two small ulcers on the penis. He reported to a physician in Los Angeles, who found the blood Wassermann four plus. The patient was given one cubic centimeter of bismuth in oil on November 5, 8, 13, 19, and 26, 1934, and 0.9 gram of neoarsphenamin on November 8, 15, and 22, 1934.

Upon admission to this hospital, physical examination revealed a very robust individual whose only positive findings were healing penile ulcers, enlargement and tenderness of the inguinal glands, and an enlarged and painful prostate. The Noguchi and cholesterin antigens were four plus; the Kahn test was positive. The patient was placed on hot sitz baths, and was given 0.1 gram of arsphenamin and 0.15 gram of bismuth salicylate on December 1 and 5, 1934. He developed a yellow tinge to the sclerae on December 6, 1934; the icteric index was 20 units. The antiluetic treatment was discontinued.

CHART 2.—*Blood Counts in Case 2*

Date	R. B. C.	W. B. C.	Hgb.	Plate	Differential	Remarks
12/9/34						Redness and swelling of gums. Temp. 100.5 F.
12/12/34	5,020,000	4,000	102%	Normal	Polys 0 S. Lymphocytes 54 L. Lymphocytes 30 Transitionals 14 Basophiles 2	Temp. 105 degrees F. Pentnucleotid. 100 I. M. twice daily.
12/19/34	5,000,000	1,800	92%	Normal	Polys 40 S. Lymphocytes 50 L. Lymphocytes 5 Transitionals 5	Temp. normal.
1/3/35	4,890,000	9,600	85%	Normal	Polys 46	Ground liver t. i. d. Up to this time a total of 390 c. c. of pentnucleotid had been given.
1/4/35	4,900,000	11,100	93%	Normal	Polys 63	Pentnucleotid discontinued.

On December 9, 1934, the patient complained of a cold and sore throat. Examination revealed redness and swelling of the gums. The temperature was 100.5 degrees Fahrenheit. Sitz baths were discontinued and the patient was treated expectantly. On December 12, 1934, the mucous membrane of the mouth was diffusely inflamed, and there was a grayish, adherent membrane over the hard palate and gums. The temperature had risen to 105 degrees Fahrenheit. Except for bilateral swelling and tenderness of the submaxillary lymph glands, the physical examination was negative. A culture of the throat smear revealed long chain streptococci and M. catarrhalis; blood culture revealed no growth. Blood counts are recorded in Chart 2.

A diagnosis of agranulocytosis was made. The patient was given normal warm saline irrigations to the throat several times daily, a liquid diet, and a sufficient amount of codein to insure rest. Pentnucleotid (10 cubic centimeters) was administered intramuscularly twice daily.

Pentnucleotid therapy was discontinued on January 14, 1935. This was followed by five doses of iodobismitol; two cubic centimeters was given intramuscularly twice a week for five doses. The percentage of granulocytes decreased from 63 to 36. Pentnucleotid was given again and the iodobismitol was discontinued. The white count returned to normal by January 27, 1935. Mercury inunctions were started and continued three times weekly. The patient felt well and was discharged as fit for duty on May 29, 1935. He was advised to continue the mercury inunctions while he felt well, and to report as an outpatient from time to time for further observation.

The following are some other points of interest in the case. The blood Wassermann test on December 17, 1934, was negative in the Noguchi and cholesterinized antigens, but positive in the Kahn. On March 7, 1935, and April 22, 1935, the blood was negative in all antigens. On May 9, 1935, the spinal fluid examination was entirely negative.

This same patient reported to the outpatient clinic one year later, on April 10, 1936, with a large furuncle on his leg. The white count was 18,000, with 80 per cent polymorphonuclears, showing that he had not suffered any permanent damage to his hemopoietic system.

COMMENT

The two cases reported from this hospital during the past year were direct results of neoarsphenamin therapy in the treatment of syphilis. In the first case here reported, both neutropenia and thrombocytopenia were outstanding findings. Furthermore, postmortem examination plus microscopic studies of the bone marrow indicated an early aplastic anemia. As would be expected from these findings, the case terminated fatally in spite of intensive therapy, consisting of pentnucleotid, liver extract, and blood transfusions.

In the second case, however, in which neutropenia was the only change in the blood picture, there was an excellent response to the pentnucleotid therapy, and the patient had completely recovered when he was discharged from the hospital.

DISCUSSION

The mechanism by which the arsphenamins cause changes in the blood picture is rather vague. Syphilis apparently has no relation to the etiology of agranulocytosis. Culley et al.[4] reported a case following neoarsphenamin therapy in which the patient was not affected with syphilis. It is a well-known fact that both benzene and arsenic cause bone-marrow depression, Kracke[5] having been able to produce agranulocytosis in rabbits by administering benzene subcutaneously; and, since arsphenamin combines these two drugs, we have a compound which may act as a very strong etiologic agent.

The cases of blood dyscrasias following the arsphenamins can be classified as follows:

Class 1. *Thrombocytopenic.* Purpura and external bleeding are constant symptoms and occur within a few hours to days after the last injection. Reduction in the number of platelets is the outstanding feature.

Class 2. *Neutropenic.* Fever, sore throat, and necrotic lesions of the pharynx are the commonest symptoms and findings clinically. The blood picture reveals a great diminution to total absence of the neutrophilic leukocyte.

Class 3. *Thrombocytopenia and Neutropenic.* Purpura, external bleeding, fever, sore throat, and necrotic lesions of the pharynx are all clinically marked. The blood picture is a combination of Classes 1 and 2—revealing a marked reduction in platelets, plus a diminution to total absence of the neutrophilic leukocyte. The red cells, hemoglobin, and lymphocytes, all remain within the normal range.

Class 4. *Aplastic.* This represents the largest group in the literature and is the most serious. The symptoms and clinical findings are varied, ranging from pallor to purpura or bleeding. The blood picture indicates a depression of all the

circulating blood elements, red cells, hemoglobin, platelets, etc.

The prognosis depends upon the amount of bone-marrow depression. The thrombocytopenic group offers the best prognosis, as they almost invariably recover when this is the only change in the blood picture. The cases of neutropenia may be expected to recover as long as there is not a total absence of polymorphonuclear cells. The group in which there is both neutropenia and thrombocytopenia offers a more serious prognosis than either of the two separate types. As shown in Case 1, which clinically fell in this group, while postmortem examination indicates a decided aplasia of the bone marrow, the prognosis may be that of aplastic anemia which, of course, is exceedingly grave, the literature revealing a mortality of 83 per cent, when, clinically, the diagnosis of true aplastic anemia was made.

IN CONCLUSION

The blood dyscrasias, although quite rare, are of sufficient interest and importance to be kept constantly in mind in any clinic where extensive antiluetic therapy is being conducted. We are reporting two cases which have occurred during the past year at the Marine Hospital in San Francisco.

Attention is called to the fact that when either purpura, external bleeding, sore throat, necrotic pharyngeal ulcerations, or pallor are present during the course of arsphenamin therapy, the blood picture should be immediately studied with one of the dyscrasias as the diagnostic possibility, and the appropriate therapy instituted without delay.†

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POTASSIUM IODID: ITS USE*

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AT eighty-four I have long been retired from active practice, but a few of my old patients still come to me for slight attention. Having specialized somewhat in diseases of the eye, I occasionally fit a pair of glasses.

So long out of practice, there would seem to be little of value which I could offer to a younger generation of physicians trained in newer methods of practice of which we scarcely dreamed. Yet it does not happen to many members of the profession to observe individuals as I have done in a few cases over a term of more than forty years. Some such observations seem worth while putting on record.

My thesis is the proper and improper use of that old and tried remedy, potassium iodid, which, as it appears to me from reports among my younger friends, is too much neglected in favor of newer drugs, often less efficient than this old reliable one. I trust I may be pardoned for a report on my personal experience.

When I was a medical student I developed a small opacity of the vitreous humor of the right eye. Doctor Frothingham of the eye department wrote me his regular prescription—a dram of iodid of potassium in an ounce of water, a teaspoonful to be taken three times a day, thus giving about seven and a half grains at each dose. I took it for about four days, when I developed an intensely sore throat and had to stop the drug. Naturally, it did no good in so short a time.

About thirty years ago this same opacity apparently increased in size so rapidly that I suspected a retinal hemorrhage. I am not sure whether the opacity actually increased in size or simply shifted its position more directly into the line of central vision. I immediately resorted to my old remedy, the iodid. Forgetful, however, of my former experience, I took ten drops of a saturated aqueous solution of the drug three times a day, about eight grains at each dose. It did splendid work with the opacity, which disappeared almost entirely within a short time, but I found my health failing so seriously that I spent about two months in bed with a rapid and irregularly acting heart and great general depression. None of our local doctors would venture a diagnosis, and I got out of bed with badly impaired health, which has greatly lessened my activities ever since.

It was about a year before any definite diagnosis was made. Then, at a meeting of the State Medical Society, I met Dr. Martin Fisher, who later went to the Medical School of the University of Cincinnati as professor of physiology. He diagnosed the case at once, assuring me that the condition was just being recognized; that there were less than a dozen cases then on record. He said that the overdosage of potassium iodid had brought on a hyperthyroidism, in my case showing only an extreme tremor and irregular heart action with depression, without the usual exophthalmia and enlargement of the thyroid. I have not kept up with medical literature for many years and the condition may be a well-recognized disease now, but it was almost unknown when I acquired it.

Curiously, I had been following a routine with all of my patients for several years which, most unfortunately, I failed to practice in my own case. I always prescribed a saturated solution of the iodid and, beginning with one, or at most, two drops, increased the dose a drop a day if there were no hurry; a drop at a dose three times daily if the case

† We wish to acknowledge the courtesy of Drs. F. C. Stewart and E. L. White, in furnishing the data on our second case.

* These personal observations by a pioneer physician of San Diego, Dr. Fred Baker, known to many of the older members of the California Medical Association, should be of interest. See also Doctor Baker's letter on page 380.